PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PZ0386-PCT	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/GB2004/005003	International filing date *(day/month/year)* 26.11.2004	Priority date *(day/month/year)* 26.11.2003

International Patent Classification (IPC) or national classification and IPC
A61K51/00

Applicant
GE HEALTHCARE LIMITED

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2005	13.03.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005003

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-56 as originally filed

   Claims, Numbers

   1-31 as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/GB2004/005003

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-30
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-30
Industrial applicability (IA)	Yes:	Claims	1-30
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

Re Item V

Reference is made to the following documents; unless otherwise indicated, reference is made to the relevant passages emphasized in the Search Report.

D1: HABERKORN UWE; KINSCHERF RALF; KRAMMER PETER H; MIER WALTER; EISENHUT MICHAEL: "Investigation of a potential scintigraphic marker of apoptosis: Radioiodinated Z-Val-Ala-DL-Asp(O-methyl)-fluoromethyl ketone" NUCLEAR MEDICINE AND BIOLOGY, vol. 28, no. 7, October 2001 (2001-10), pages 793-798, XP002333221

D2: DECKWERTH ET AL: "Long-term protection of brain tissue from cerebral ischemia by peripherally administered peptidomimetic caspase inhibitors" DRUG DEVELOPMENT RESEARCH, vol. 52, no. 4, April 2001 (2001-04), pages 579-586, XP002333222

D3: WO 01/89584 A (NYCOMED IMAGING AS; KLAVENESS, JO; TOLLESHAUG, HELGE; AMERSHAM HEALTH) 29 November 2001 (2001-11-29)

D4: US-B1-6 589 503 (PIWNICA-WORMS DAVID) 8 July 2003 (2003-07-08)

D5: BHARATHI ET AL: "Noninvasive real-time imaging of apoptosis." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATE OF AMERICA, vol. 99, no. 26, 24 December 2002 (2002-12-24), pages 16551-16555, XP002333223

D6: WO 2004/069773 A (MERCK FROSST CANADA & CO; COLUCCI, JOHN; GIROUX, ANDRE; HAN, YONGXIN;) 19 August 2004 (2004-08-19)

1. Novelty

The subject-matter of the present set of claims appears not to be disclosed in the cited prior art (Art. 33(2) PCT).

2. Inventive step

- The claimed caspase-3 inhibitors were all known before the priority date of the application.

  Since D1 already discloses the use of a [^{131}I]IZ-VAD-fmk for monitoring apoptosis the substitution of ^{131}I with other "imaging moieties" or the substitution of Z-VAD-fmk with other caspase-3 inhibitors can only be regarded as technically equivalent alternatives of the teaching of D1.

Claims 1-30 therefore do not contain technical features which could justify the recognition of inventive merits in the light of D1. These claims therefore lack an inventive step (Art. 33(3) PCT).

- Moreover, D3-D5 disclose imaging agents which comprise a peptidic recognition moiety of caspase-3 (DEVD) and an imaging moiety. The agents are used for in vivo determination of activated caspase-3 and for monitoring apoptosis.
It is explicitly stated that "...because most cells activate caspase-3 during apoptosis..." (D5, page 16551, left-hand column), the agents are synthesized as "...novel molecular-based reporter for noninvasive detection of apoptosis...".

D4 states that "...rapid clearance of the complexes from non-target cells and tissues of the body would facilitate and enhance the utility of such complexes in vivo" (column 7 lines 42-45) and proposes the use of labelled caspase-3 substrates to solve this problem.

Thus, it was known before the priority date that caspase-3 is a potential target for imaging agents for the detection of apoptosis and the rapid clearance of the compounds from tissue was known as well.

The difference between D3-D5 and the application is the use of caspase-3 INHIBITORS rather than substrates.
However, no technical effect can be regarded from this substitution and the proposed solution cannot be regarded to be inventive.

Claims 1-31 therefore lack an inventive step (Art. 33(3) PCT).

Re Item VI

Certain documents cited

D6 (WO2004/069773) could become relevant in some contracting states.